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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/509,261 | 05/20/2005 | Michael Ploch | 166-76 | 5306 |

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| EXAMINER | |
|---|---|
| CLARK, AMY LYNN | |

| ART UNIT | PAPER NUMBER |
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| 1655 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| **Advisory Action Before the Filing of an Appeal Brief** | **Application No.** 10/509,261 | **Applicant(s)** PLOCH ET AL. | |
|---|---|---|---|
| | **Examiner** Amy L. Clark | **Art Unit** 1655 | |

***--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --***

THE REPLY FILED 19 October 2007 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires *3* months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *18,20-25,30 and 34-39*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

Michele C. Flood

MICHELE FLOOD
PRIMARY EXAMINER

Continuation of 11. does NOT place the application in condition for allowance because: Newly amended claims 18, 20-25, 30 and 34-39 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

This rejection is maintained for reasons of record set forth in the paper mailed on 17 July 2007 and repeated below, slightly altered to take into consideration Applicant's amendment filed on 19 October 2007.
Applicant's arguments have been thoroughly considered, but the rejection remains the same for the reasons set forth in the previous Office action and for the reasons set forth below.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the Invention: The claims are drawn to a method for treating schizophrenia, comprising administering a therapeutically effective amount of a pharmaceutical composition comprising: at least one medicament comprising at least on extract selected from the group consisitng of an extract of Hypericum perforatum (St. John's wort), an extract of Crocus Sativus (saffron), and an extract of Panax ginseng (ginseng); and a pharmaceutically acceptable carrier.

Breadth of the Claims: The claims are broad in that a therapeutically effective amount of a pharmaceutical composition comprising: at least one medicament comprising at least on extract selected from the group consisitng of an extract of Hypericum perforatum (St. John's wort), an extract of Crocus Sativus (saffron), and an extract of Panax ginseng (ginseng); and a pharmaceutically acceptable carrier may be administered to treat schizophrenia in a patient. The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims.

Guidance of the Specification and Existence of Working Examples: The specification describes a method for measuring the ketamine-antagonistic effect of hypericum extract as a parameter that shows a possible effectiveness of St John's wart (Jarsin® 750 mg, Lichtwer Pharma AG, Berlin, Germany) on the negative symptoms of patients with chronic schizophrenia (See pages 9-11).

The specification envisions that a pharmaceutical composition comprising: at least one medicament comprising at least on extract selected from the group consisitng of an extract of Hypericum perforatum (St. John's wort), an extract of Crocus Sativus (saffron), and an extract of Panax ginseng (ginseng); and a pharmaceutically acceptable carrier will have utility in humans in treating schizophrenia. However, no working examples are provided with regard to a method for treating schizophrenia. Furthermore, no working examples are provided that demonstrate the efficacy of a pharmaceutical composition comprising: at least one medicament comprising at least on extract selected from the group consisitng of an extract of Hypericum perforatum (St. John's wort), an extract of Crocus Sativus (saffron), and an extract of Panax ginseng (ginseng); and a pharmaceutically acceptable carrier in the treatment of schizophrenia.

Predictability and State of the Art: The state of the art at the time the invention was made was unpredictable and underdeveloped. For example, Akhondzadeh The 5-HT hypothesis of schizophrenia'. Drugs, Vo. 4, no. 3 (Mar 2001), pp 295-300. PubMed Abstract) teaches that early theories of schizophrenia implicated disturbed serotonin (5-HT) neurotransmission, but these were largely overshadowed by the dopamine theory of schizophrenia, which became established after the introduction of chlorpromazine, however, the importance of 5-HT in CNS function is once again being recognized. Akhondzadeh further teaches that the ability of antipsychotic drugs to diminish positive symptoms has been correlated with their ability to block dopamine D(2) receptors, although negative symptoms are not as effectively treated by typical neuroleptics and that there is increasing interest in the correlation between negative symptoms of schizophrenia and 5-HT(2) receptors. Akhondzadeh further teaches that the rationale for these studies is the hypothesis that abnormal neurotransmission at 5-HT(2) receptors may be involved in the pathophysiology of schizophrenia. Therefore, the exact cause of schizophrenia is not currently known and how to treat negative symptoms is not currently understood completely. Lal et al. ( 'St. John's wort and schizophrenia.' Canadian Medical Association Journal, Vol. 163, no. 3 (August 8, 2000), pp. 262-263) teaches that 2 patients with schizophrenia experienced psychotic relapse that was temporally associated with the consumption of St. John's wort (See page 263).
Thus, while the claim-designated method may be useful for providing such an effect, Applicant does not disclose a method comprising the administration of compositions comprising: at least one medicament selected from the group consisting of Hypericum perforatum (St. John's wort), Gingko biloba (gingko), Crocus Sativus (saffron), Panax ginseng (ginseng) and pharmaceutical acceptable salts thereof for treating schizophrenia. The Office further notes that while the specification discloses that the claim-designated method will have utility in humans in treating schizophrenia, nowhere in the specification or in the limitations does Applicant direct the claimed subject matter to the administration of a pharmaceutical composition comprising: at least one medicament comprising at least on extract selected from the group consisitng of an extract of Hypericum perforatum (St. John's wort), an extract of Crocus Sativus (saffron), and an extract of Panax ginseng (ginseng); and a pharmaceutically acceptable carrier to any subject.

Amount of Experimentation Necessary: The quantity of experimentation necessary to carry out the claimed invention is high, as the skilled artisan could not rely on the prior art or instant specification to teach how to make and use a pharmaceutical composition comprising: at least one medicament comprising at least on extract selected from the group consisitng of an extract of Hypericum perforatum (St. John's wort), an extract of Crocus Sativus (saffron), and an extract of Panax ginseng (ginseng); and a pharmaceutically acceptable carrier in the treatment of schizophrenia in humans. In order to carry out the claimed invention, one of ordinary skill in the art would have to identify a pharmaceutical composition comprising: at least one medicament comprising at least on extract selected from the group consisitng of

an extract of Hypericum perforatum (St. John's wort), an extract of Crocus Sativus (saffron), and an extract of Panax ginseng (ginseng); and a pharmaceutically acceptable carrier that can be administered in a therapeutically effective dose with an acceptable level of side-effects.
In view of the breadth of the claims and the lack of guidance provided by the specification as well as the unpredictability of the art, the skilled artisan would have required an undue amount of experimentation to make and/or use the claimed invention. Therefore, Claims 18, 20-25, 30 and 34-39 are not considered to be fully enabled by the instant specification.

Applicants argue that the claims, as amended, provide a clear teaching of what the pharmaceutical composition of the present invention comprises and that this teaching, as well as the discussion of a full working example on pages 9 to 11 of the English translation of the International Application which discusses the pharmaceutical effectiveness of the present invention, fully enables the present invention and that given the relatively high level of skill of one skilled in the art, the clear claim language as amended and the teaching on how to realize the present invention discussed above, it is respectfully submitted that the claims as amended are fully enabled by the instant specification.

However, this is not found persuasive because first of all, Applicants have not provided any working examples showing that an extract of Crocus sativus or an extract of Panax ginseng have any effect on schizophrenia. Secondly, Applicants have cited two references on pages 9-11 of the originally filed specification: Butterweck et al., 1997 (V. Butterweck, A. Wall, U. Lieflander-Wulf, H. Winterhoff and A. Nahrstedt, Effects of the total extract and fractions of Hypericum perforatum in animal assays for antidepressant activity, Pharmacopsychiatry 30 (1997) (Suppl. 2), pp. 117-124) and Duncan G. et al [(2000) J Pharmacol Exp Ther 293:8-14, Krystal J-H, et al (2000): Biol Psychiatry 47:137-143], which Applicants appear to include to draw a correlation between the effects of ketamine (Duncan G. et al.) and the effects of St John's wort (Butterweck V. et al.), which Applicants argue are suitable references to establish enablement. However, Duncan et al. simply teach that the ability of subanesthetic doses of N-methyl-D-aspartate antagonists may contribute to the pathophysiology of schizophrenia (See abstract) but that it is not proven to be the case, and in the Butterweck reference, St. John's wort is being used to study possible antidepressent activity, which is not the same as studying the effect of St. John's wort on schizophrenia, since depression and schizophrenia are two completely different psychological diseases and require completely different courses of treatment. Finally, Applicants provide a study wherein 16 healthy people were provided with either a placebo or an extract of St. John's wort and the subjects are given ketamine and the effect of a placebo and the effect of extracts of St. John's wort were measured. This in no way provides any insight into the effects of of an extract of Hypericum perforatum (St. John's wort), an extract of Crocus Sativus (saffron), or an extract of Panax ginseng (ginseng) on people suffering from schizophrenia or effects of schizophrenia. Furthermore, the art at the time the invention was made taught that the exact cause of schizophrenia was not known and how to treat negative symptoms was not understood completely. Moreover, the art taught that Lal 2 patients with schizophrenia experienced psychotic relapse that was temporally associated with the consumption of St. John's wort, thereby showing that St. John's wort has the opposite effect of that claimed by Applicant. .